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Cytokines

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ABSTRACT

The term cytokine encompasses a large and diverse family of polypeptide regulators that are produced widely throughout the body by cells of diverse embryological origin. Cytokines participate in many physiological processes including the regulation of immune and inflammatory responses. Cytokines include chemokines, interferons, interleukins, lymphokines, tumor necrosis factor but generally not hormones or growth factors. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells, a given cytokine may be produced by more than one type of cells. They act through receptors, and are especially important in the immune system, cytokines modulate the balance between humoral and cell-based immune responses and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways.

Cytokines are also serving as cell-signaling protein molecules used extensively in intercellular communication. Cytokines can be classified as proteins, peptides, or glycoproteins. The term “cytokine” encompasses a large and diverse family of regulators produced throughout the body

by cells of diverse embryological origin. Each cytokine has a matching cell-surface receptor, its activation leads to cascades of intracellular signaling that alter cell functions. This may include the up regulation and/or down regulation of several genes and their transcription factors, resulting in the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition.

Keywords: Cytokines; Immune System; Receptor; Diagnosis; Treatment.

DEFINITION

Cytokines (Greek cyto-, cell; and -kinos, movement) are a category of signaling molecules that are used extensively in cellular communication. They are proteins, peptides, or glycoproteins. They are a broad and loose category of small proteins (~5– 20 kDa) that are important in cell signaling [1]. Cytokines are released by cells and affect the behavior of other cells, and sometimes releasing cell itself. Cytokines include chemokines, interferons, interleukins, lymphokines, tumor necrosis factor but generally not hormones or growth factors [2]. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cells [3,4]. They act through receptors, and are especially important in the immune system, cytokines modulate the balance between humoral and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways [4]. Some cytokines are chemical switches that turn certain immune cell types on and off. They include a diverse assortment of interleukins, interferons, and growth factors [2]. They are important in health and disease, specifically in host responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction [5]. Interleukin 2 (IL-2), triggers the immune system to produce T cells. IL-2's immunity-boosting properties have traditionally made it a promising treatment for several illnesses [6].

Some cytokines chemically attracts specific cell types which are called chemokines [7]. These chemokines are released by cells at a site of injury or infection and call other immune cells to the region to help repair the damage or fight off the invader [8]. The chemokines play a key role in inflammation process and have a promising target for new drugs to help regulate immune responses [9].

Cytokines are also serve as cell-signaling protein molecules used extensively in intercellular communication. Cytokines can be classified as proteins, peptides, or glycoproteins. The term "cytokine" encompasses a large and diverse family of regulators produced throughout the body by cells of diverse embryological origin [10]. Each cytokine has a matching cell-surface receptor, its

activation leads to cascades of intracellular signaling that alter cell functions. This may include the up regulation and/or down regulation of several genes and their transcription factors, resulting in the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition [11].

Adverse effects of cytokines have been linked to many disease states and conditions ranging from major depression and Alzheimer's disease to cancer with levels either being elevated or changed. Plasma levels of various cytokines may give information on the presence, or even predictive value of inflammatory processes involved in autoimmune diseases [12].

Lymphokines are a subset of cytokines that are produced by a type of immune cells known as lymphocytes. They are protein mediators typically produced by T cells to direct the immune system response by signaling between its cells. Lymphokines have many roles, including the attraction of other immune cells, macrophages, and other lymphocytes, to an infected site and their subsequent activation to prepare them to mount an immune response. Circulating lymphocytes can detect a very small concentration of lymphokines and then move up the concentration gradient towards where the immune response is required [13].

DISCOVERY

Interferon-alpha, an interferon type I, was identified in 1957 as a protein that interfered with viral replication [14]. The activity of interferon-gamma (the sole member of the interferon type II class) was described in 1965; this was the first identified lymphocyte-derived mediator [15,16]. Macrophage migration inhibitory factor (MIF) was identified simultaneously in 1966 by Bloom and Bennett [17]. In 1969 Dudley Dumonde proposed the term "lymphokine" [18] to describe proteins secreted from lymphocytes [19] and later, proteins derived from macrophages and monocytes in culture were called "monokines" [20]. It was understood that these proteins and others were part of a broader class of proteins involved in self-defense, and should be called "cytokines" [21].

NOMENCLATURE

Cytokines are released by cells of the immune system, especially by monocytes and T lymphocytes [1], but they are also secreted by many cells in addition to those of the immune system, such as endothelial cells and fibroblasts. They used to have different names depending either on their origin, such as lymphokines (produced by lymphocytes), monokines (monocytes) or on their activity: chemokines, interleukins, interferon [22]. The term "cytokine" has been used to refer to the immunomodulating agents, such as interleukins and interferons [23].

The interleukin nomenclature was invented to deal with the issue of multiple biological properties. At the time of the naming, these molecules with an interleukin number and primary amino acid sequences of the active molecules were not known [24,25]. The term IL-1 was used to define a monocyte product and the term IL-2 was used to define a lymphocyte product [24].

But the nomenclature did nothing to resolve the broader issue of multiple biological properties ascribed to a single molecule. IL-1 was reported to cause fever, induce acute phase protein synthesis, activate B-cells and act as a co-factor for T-cell proliferation in the presence of antigens or mitogens [26,27]. IL-2 was reported to expand T-cell proliferation and also activate B-cells. IL-2 was initially termed T-cell growth factor and expanded human T-cells in vitro [28].

Liles and Van Voorhis [29] reviewed 42 cytokines and interleukins that are involved in inflammatory and immune responses. The cytokines are as hematopoietic growth factors, interferons, lymphokines, monokines, chemokines, and other cytokines.

The term interleukin was initially used by researchers for those cytokines whose presumed targets are principally leukocytes. It is now used for designation of newer cytokine molecules and bears little relation to their presumed function. The vast majority of these are produced by T-helper cells [13].

- Lymphokines, produced by lymphocytes
- Monokines, produced exclusively by monocytes
- Interferons, involved in antiviral responses
- Colony stimulating factors, support the growth of cells in semisolid media
- Chemokines mediate chemo-attraction (chemotaxis) between cells [30].

CLASSIFICATION

The classification based on the cell of origin or the function, their spectrum of activity, the category of activity they influence, the cells that are their targets, or on specific features of their ligand-receptor interaction [31] , The knowledge of structural and functional aspects of cytokines has been extraordinarily developed, especially in the human and murine species [32].

Classification According to Structure

Structural homology has been able to partially distinguish between cytokines that do not demonstrate a considerable degree of redundancy so that they can be classified into four types [33]. Structures of whose members have four bundles of α-helices. This family in turn is divided into three sub-families, the IL-2 subfamily, the interferon (INF) subfamily and the IL-10 subfamily. The first of these three subfamilies is the largest, and contains several non-immunological cytokines including erythropoietin (EPO) and thrombopoietin (THPO) [34]. IL-1 family, which primarily includes IL-1 and IL-18. IL-17 family, which is yet to be completely characterized. However, it is known that they have a specific effect in promoting proliferation of T-cells that cause cytotoxic effects [35].

Classification According to Function

A classification that proves more useful in clinical and experimental practice is dividing cytokines into those that enhance cellular immune responses, type 1 (IFN-γ, TNFα, etc.), and type 2 (TGF-β, IL-4, IL-10, IL-13, etc.), which favor antibody responses [36]. A key focus of interest has been that cytokines in one of these two subsets tend to inhibit the effects of those in the other. Dysregulation of this tendency is under intensive study for its possible role in the pathogenesis of autoimmune disorders [37].

Some cytokines are primarily lymphocyte growth factors; others function as proinflammatory or anti-inflammatory molecules whereas other cytokines polarize the immune response to antigen. Cytokines have become an important frontier in medicine in a vital place as diagnostic, prognostic and therapeutic agents in human disease [24].

Several inflammatory cytokines are induced by oxidative stress [38-40]. The fact that cytokines themselves trigger the release of other cytokines [41-43] and also lead to increased oxidative stress makes them important in chronic inflammation, as well as other immune responses, such as fever and acute phase proteins of the liver (IL-1,6,12, IFN-a) [43].

Interferon-γ (IFNγ), essential for defense against several intracellular microorganisms such as *Mycobacterium tuberculosis,* is also a major cytokine in the pathogenesis of several autoimmune diseases. IL-2 is needed for the generation of cytotoxic T-cells (CTL) and forms the basis for several vaccines but the same cytokine drives graft versus host disease and limits the success of bone marrow transplantation.

IL-1, as its properties ranged from effects on control of body temperature to liver protein synthesis to T-cell responses to antigens and mitogens [24].

THE CYTOKINE RECEPTORS

The cytokine receptors are membrane glycoproteins consisting of several units. They have the role of internalization of the signal. Cytokines usually act locally, both in the cells producing them (autocrine activity) and in the cells next to it (paracrine activity). More rarely they have an effect on cells and tissues distant from the place where they are produced (endocrine activity). However, some cytokines, especially those with inflammatory effects such as IL-1 and TNF, have their effect after being transported through the blood to distant target cells. Several types of cytokines have been newly described, and some of them have been cloned. For example, in the human and murine species 36 cytokines have been cloned, although only 19 are available from the porcine species [44]. Number of cloned cytokines in different species is illustrated in table 1.

Table 1: Number of Cloned Cytokines.

Human and murine species:	36
Bovine species:	23
Ovine species:	20
Porcine species:	19
Feline and equine species:	11
Avian species:	7
Canine species:	5
Fish species:	4

CLONED	CYTOKINES
TNF-α (1989)	TGFβ2 (1993)
IL-1-α (1990)	TGFβ3 (1988)
IL-1-β (1993)	AMCF-II (1992)
IL-2 (1991)	IL-12 (1997)
IL-4 (1993,1994)	IL-15 (1998)
IL-6 (1991,1992,1993,1994)	GSC-F (1995)
IL-8 (1994,1992)	VEG-F (1995)
TGFβ1 (1992)	GM-CSF (1995)

The cytokines IL 2, IL 4, IL 7, IL 9 and IL 15 share the same receptors and have a common function. They have a g chain receptor (gc CD 123) which is related to the activation of the T lymphocytes growth. Cytokines IL 3, IL 5 and GM-CSF share the receptor of the b chain (bc) which is related to the proliferation and differentiation of the hematopoietic precursors. The cytokine membrane receptors are demonstrated in table 2.

Table 2: Classification of cytokine membrane receptors.

Receptors of the hematopoietin receptor family. They belong to the family of receptors a, b and g. The following cytokines have been includedin this group: IL 2, IL 3, IL 4, IL 5, IL 6, IL7, IL 9, IL 13, IL 15, GM-CSF (Granulocyte Macrophage Colony-Stimulating Factor) and G-CSF (Granulocyte- Colony Stimulation Factor).
Interferon receptors. They have receptors a and b. IFNa, IFNb and IFNg belong to this family.
Transforming Growth Factors (TGF). TGFa and TGFb belong to this family.
Tumor Necrosis Factor (TNF) Receptors: (TNFa) and (TNFb).
Receptors for the immunoglobulin superfamily: IL 1a, IL 1b, IL 16 belong to this family.
Chemokine Receptors (seven-part receptors): IL 8, Platelet-Activating Factor (PAF).

Pro-inflammatory cytokines and chemokines, including IL-1, IL-6, IL-8, and TNF-alpha establish an environment that promotes disease progression [45]. These cytokines and chemo attractants are secreted not only by immune regulatory cells, but also by tumor cells, tumor-associated macrophages, and stromal cells. In addition, tumor-associated cells secrete growth factors, such as VEGF and FGF basic, and matrix-degrading proteases [46].

gAdiponectin/gAcrp30	IL-12/IL-23 p40
AdipoR1	IL-12 R beta 1
AdipoR2	IL-12 R beta 2
Amphiregulin	IL-12/IL-35 p35
EGF	IL-13
EGF R/ErbB1	IL-13 R alpha 1
EMAP-II	IL-13 R alpha 2
G-CSF	IL-18/IL-1F4
GM-CSF	IL-18 R alpha/IL-1 R5
HB-EGF	IL-18 R beta/IL-1 R7
HGF	IL-20 R alpha
HGF Activator	IL-20 R beta
HGF R/c-MET	IL-22 R alpha 1
IFN-alpha	IL-24
IFN-alpha/beta R1	IL-6/IL-6 R alpha Complex
IFN-alpha/beta R2	LAP (TGF-beta 1)
IFN-beta	Leptin/OB
IFN-gamma	Leptin R
IFN-gamma R1/CD119	MIF
IFN-gamma R2	Oncostatin M/OSM
IL-1 alpha/IL-1F1	PBEF/Visfatin
IL-1 beta/IL-1F2	TGF-alpha
IL-1ra/IL-1F3	TGF-beta
IL-1 RI	TGF-beta 1
IL-1 RII	TGF-beta 1, 2, 3
IL-1 RAcP/IL-1 R3	TGF-beta 2
IL-4	TGF-beta 3
IL-4 R alpha	TGF-beta RI/ALK-5
IL-6	TGF-beta RII
IL-6 R alpha	TGF-beta RIII
IL-10	TNF-alpha
IL-10 R alpha	TNF RI/TNFRSF1A
IL-10 R beta	TNF RII/TNFRSF1B

CYTOKINES ACTION

The cytokines can act as:

- Mediators of the innate immunity (inflammation, chemotaxis, macrophage activation, NK cells) and adaptive immunity (humoral and cellular) [47].
- Regulators of lymphocyte activation, proliferation and differentiation [26].
- Stimulators of the growth of hematopoietic stem cells [48].

Cytokines production and release from innate immune cells are critical responses to inflammation and infection. Populations of white blood cells as circulating dendritic cells, monocytes, natural killer (NK) cells, neutrophils, eosinophils, basophils, tissue-resident mast cells and macrophages comprise innate immune cells [49,50]. These cells control opportunistic invasion with a range of pathogens as viruses, bacteria, fungi and parasites [50]. Cytokine release can be directly evoked by immunoglobulin- or complement receptor-mediated signaling or by pathogens through a diverse array of cellular receptors, including pattern recognition receptors such as TLRs [51,52]. The Gram-negative bacterial coat component lipopolysaccharide (LPS), the main culprit behind toxic shock syndrome and sepsis, is a highly potent trigger of cytokine secretion through TLR4 [50].

Most cytokines rely on membrane-bound and cytoplasmic cellular proteins, the so-called trafficking machinery, to mediate their transport through the cell [52-54]. Cytokines are released by cells into the circulation or directly into tissues. The cytokines locate target immune cells and interact with receptors on the target immune cells by binding to them. The interaction triggers or stimulates specific responses by the target cells [55,56].

Among the best studied of the trafficking machinery proteins in cytokine release are the membrane fusion proteins known as SNAREs [57]. The SNAREs include subfamilies of vesicle-associated membrane proteins (VAMPs) and syntaxins which are classified by the amino acid composition of their core SNARE domains as RSNAREs and Q-SNAREs, respectively. Typically, Q- and R-SNAREs on opposing target and vesicle membranes unite as a 4-helix coiled-coil bundle that winches tethered membranes together for fusion [58,59].

The mode of action of many of the cytokines involves typical signal transduction events such as protein phosphorylation. The role in other pathologic processes has provided insight into autoimmune and allergic diseases, as well as a variety of systemic disorders. Because of their broad spectrum of activity, cytokines have been used in a variety of therapeutic settings involving both infectious diseases and neoplasia [31].

Immunohistologic examination of mature peripheral blood neutrophils suggests that TGFα, TNF, IL-6, IL-12, and CXCL2/IL-8 are stored within peroxidase-negative organelles [60-62]. Neutrophils produce a wide range of cytokines and chemokines, and their precise intracellular locations are not known [59,63,64]. Basophils are another granulocyte that is important in the generation of cytokines, particularly IL-4 in allergic inflammation [65].

Mast cells, which are important innate immune cells in allergy and inflammatory diseases that reside in tissues, secrete numerous cytokines and chemokines, many of which are stored as preformed mediators in their secretory granules [66]. Cytokines are released during classical degranulation, shown by the rapid secretion of IL-4 and TNF during receptor-mediated exocytosis by cross-linking cell surface complexes of IgE and Ag [67-70]. Moreover, mast cell granules contain chemokine receptors CCR3 and CXCR2 [71,72].

Major effector cell in allergy and asthma is the eosinophil, which can release ≤ 35 different cytokines, chemokines, and growth factors [73,74]. Eosinophils were shown to traffic Th1 (IFNγ, IL-12) and Th2 cytokines (IL4, IL-13), as well as TNF, IL-6, and IL-10, through a tubulovesicular system and small secretory vesicles that bud from the crystalloid granules, and that serve to shuttle cytokines from the granules to the cell membrane [75,76]. A potent chemokine that triggers chemotaxis in eosinophils, IL-4 is transported through the tubulovesicular system and small secretory vesicles [77].

Other innate immune cells also express cytokine receptors in their intracellular granules. In particular, neutrophils secrete IL-10 [78] and express IL-10 receptor in association with their specific granules [79]. NK cells are cytotoxic cells of the innate immune system to kill virally infected or tumorigenic target cells. Similar to mast cells and eosinophils, cytokine release in NK cells is mediated independently of lytic granules [80].

TNF is a potent proinflammatory cytokine secreted by many innate immune cells, particularly activated macrophages, but also neutrophils, mast cells, eosinophils, dendritic cells, and NK cells [60,61,67,81,82]. Macrophages also produce and secrete a cascade of other proinflammatory and anti-inflammatory cytokines, such as IL-6, IL-10, IL-12, and a host of chemokines that are trafficked and secreted by constitutive exocytosis, moving, sometimes simultaneously, through the ER and Golgi complex [60,81-83]. The proinflammatory cytokine IL-1β is one of the most crucial mediators of inflammation and host responses to infection [84].

CYTOKINE ACTIVITIES

Cytokines are made by many cell populations, but the predominant producers are helper T cells (Th) and macrophages. Cytokines stimulate immune cell proliferation and differentiation [85]. They include Interleukin 1 (IL-1), which activate T cells [86], IL-2, which stimulate the proliferation of antigen-activated T and B cells [87], IL-4, IL-5, and IL-6, which stimulate proliferation and differentiation of B cells [88], interferon gamma(IFN γ) which activates macrophages [89] and IL-3, IL-7 and Granulocyte Monocyte Colony Stimulating Factor (GM-CSF), which stimulate hematopoiesis [90].

Other groups of cytokines include interferons and chemokines. Interferons IFNα and IFNβ inhibit virus replication in infected cells [91], while IFNγ also stimulates antigen-presenting cell MHC expression [91]. Chemokines attract leukocytes to infection sites. Chemokines have conserved cysteine residues that allow them to be assigned to four groups [93]. The groups, with representative chemokines, are C-C chemokines (RANTES, MCP-1, MIP-1α, and MIP1β), C-X-C chemokines (IL-8), C chemokines (Lymphotactin), and CXXXC chemokines (Fractalkine). Some cytokines are predominantly inhibitory. For example, IL-10 and IL13 inhibit inflammatory cytokine production by macrophages [94].

Helper T cells have two important functions: to stimulate cellular immunity and inflammation, and to stimulate B cells to produce antibodies [95]. Two functionally distinct subsets of T cells secrete cytokines which promote these different activities [96]. Th1 cells produce IL-2, IFNγ, and TNFβ, which activate Tc and macrophages to stimulate cellular immunity and inflammation [97]. Th1 cells also secrete IL-3 and GM-CSF to stimulate the bone marrow to produce more leukocytes [98]. Th2 cells secrete IL-4, IL-5, IL-6, and IL-10, which stimulate antibody production by B cells [99].

T cells are initially activated as Th0 cells, which produce IL-2, IL-4 and IFNγ. The nearby cytokine environment then influences differentiation into Th1 or Th2 cells. IL-4 stimulates Th2 activity and suppresses Th1 activity, while IL-12 promotes Th1 activities. Th1 and Th2 cytokines are antagonistic in activity [100]. Th1 cytokine IFNγ inhibits proliferation of Th2 cells, while IFNγ and IL-2 stimulate B cells to secrete IgG2a and inhibit secretion of IgG1 and IgE. Th2 cytokine IL-10 inhibits Th1 secretion of IFNγ and IL-2, it also suppresses Class II MHC expression and production of bacterial killing molecules and inflammatory cytokines by macrophages [101]. IL-4 stimulates B cells to secrete IgE and IgG1. The balance between Th1 and Th2 activity may steer the immune response in the direction of cell-mediated or humoral immunity [102].

Table 3: Selected immune cytokines and their activities*.

Cytokine	Producing Cell	Target Cell	Function**
GM-CSF	growth and Th cells progenitor monocytes and DC	differentiation of Cells	
IL-1α	monocytes	Th cells	co-stimulation
	macrophages	B cells	maturation and proliferation
IL-1β	B cells DC	NK cells	Activation
		Various	Inflammation, acute phase response, fever
IL-2	Th1 cells	activated T and B cells, NK cells	growth, proliferation, activation
IL-3	Th cells NK cells	stem cells	growth and differentiation
		mast cells	growth and histamine release
IL-4	Th2 cells	activated B cells	proliferation and differentiation IgG_1 and IgE synthesis
		macrophages	MHC Class II
		T cells	Proliferation
IL-5	Th2 cells	activated B cells	proliferation and differentiation IgA synthesis
IL-6	monocytes	activated B cells	differentiation into plasma cells
		plasma cells	antibody secretion
	macrophages	stem cells	Differentiation
	Th2 cells stromal cells	various	acute phase response
IL-7	marrow stroma	stem cells	differentiation into progenitor B and T cells
	thymus stroma		
IL-8	macrophages	neutrophils	Chemotaxis
	endothelial cells		
IL-10	Th2 cells	macrophages	*cytokine production*
		B cells	Activation
IL-12	macrophages	activated Tc cells	differentiation into CTL (with IL-2)
	B cells	NK cells	Activation
IFN-α	leukocytes	various	*viral replication*
			MHC I expression
IFN-β	fibroblasts	various	*viral replication*
			MHC I expression

IFNγ Tc	Th1 cells, NK cells	various	*Viral replication*
		macrophages	MHC expression
		activated B cells	Ig class switch to IgG_{2a}
		Th2 cells	*Proliferation*
		macrophages	pathogen elimination
MIP-1α	macrophages	monocytes, T cells	Chemotaxis
MIP-1β	lymphocytes	monocytes, T cells	Chemotaxis
TGF-β	T cells, monocytes	monocytes, macrophages	Chemotaxis
		monocytes, macrophages	Chemotaxis
		activated macrophages	IL-1 synthesis
		activated B cells	IgA synthesis
		various	*proliferation*
TNFα	macrophages, mast cells, NK cells	tumor cells	cell death
		phagocytes	phagocytosis, NO production
		tumor cells	cell death

CYTOKINE RECEPTORS

Cytokines act on their target cells by binding specific membrane receptors. The receptors and their corresponding cytokines have been divided into several families based on their structure and activities. Hematopoietin family receptors are dimers or trimers with conserved cysteines in their extracellular domains and a conserved TrpSer-X-Trp-Ser sequence. Interferon family receptors have the conserved cysteine residues but not the Trp-Ser-X-Trp-Ser sequence, and include the receptors for IFNα, IFNβ, and IFNγ [104]. Tumor Necrosis Factor family receptors have four extracellular domains; they include receptors for soluble TNFα and TNFβ as well as membrane-bound CD40 (important for B cell and macrophage activation) and Fas (which signals the cell to undergo apoptosis) [105]. Chemokine family receptors have seven transmembrane helices and interact with G protein. This family includes receptors for IL-8, MIP-1 and RANTES. Chemokine receptors CCR5 and CXCR4 are used by HIV to preferentially enter either macrophages or T cells [105].

Hematopoietin cytokine receptors have two subunits, one cytokine-specific and one signal transducing [106]. An example is the GM-CSF subfamily, where a unique α subunit specifically binds either GM-CSF, IL-3, or IL-5 with low affinity and a shared β subunit signal transducer also increases cytokine-binding affinity. Cytokine binding promotes dimerization of the α and β subunits, which then associate with cytoplasmic tyrosine kinases to phosphorylate proteins which activate mRNA transcription. GM-CSF and IL-3 act on hematopoietic stem cells and progenitor cells and activate monocytes. With IL-5, they also stimulate eosinophil proliferation and basophil degranulation. All three receptors phosphorylate the same cytoplasmic protein. Antagonistic GM-CSF and IL-3 activities can be explained by their competition for limited amounts of β subunit [104].

The IL-2R subfamilies of receptors for IL-2, IL-4, IL-7, IL-9, and IL-15 have a common signal-transducing γ chain. Each has a unique cytokine-specific α chain. IL-2 and IL-15 are trimers, and share an IL-2R β chain. Monomeric IL-2R α has low affinity for IL-2, dimeric IL-2R αβ has intermediate affinity, and trimeric IL-2R αβγ binds IL-2 with high affinity. IL-2Rα chain (Tac) is expressed by activated but not resting T cells. Resting T cells and NK cells constitutively express low numbers of IL-2R βγ [104]. Antigen activation stimulates T cell expression of high affinity

IL-2R trimers as well as secretion of IL-2, allowing autocrine stimulation of T cell proliferation in an antigen-specific manner. Antigen specificity of the immune response is also maintained by the close proximity of antigen-presenting B cells and macrophages with their helper T cells, so that cytokines are secreted in the direction of and close to the membrane of the target cell. X-linked severe combined immunodeficiency (X-scid) is caused by a defect in IL-2R family γ chain, which results in loss of activity from this family of cytokines [107].

Cytokine activity can be blocked by antagonists, molecules which bind cytokines or their receptors [108]. IL-1 has a specific antagonist that blocks binding of IL-1α and IL-1β to their receptor. During immune responses, fragments of membrane receptors may be shed and then compete for cytokine binding. Microbes also influence cytokine activities. For example, Vaccinia virus (Smallpox and Cowpox) encodes soluble molecules which bind IFNγ, while Epstein-Barr virus (Infectious Mononucleosis) encodes a molecule homologous to IL-10 that suppresses immune function in the host [109].

The TNF receptor family molecules CD40 and Fas bind cell surface ligands on effector T cells: CD40L and FasL. CD40 is expressed on B cell and macrophage plasma membranes [110]. T cell CD40L binding to B cell CD40 stimulates B cell proliferation and isotype switching. T cell CD40L binding to macrophage CD40 stimulates macrophages to secrete TNFα and become much more sensitive to IFNγ. T cell FasL binding to Fas leads to the activation of caspase proteases that initiate apoptosis of the cell expressing membrane Fas. Activated lymphocytes express Fas, so that FasL-positive Tc cells can regulate the immune response by eliminating activated cells [104]. An immune deficiency disease linked to expression of a mutant Fas is characterized by over-proliferation of lymphocytes [111].

FUNCTION OF CYTOKINES

Cytokines play a variety of regulatory roles in both host defense and normal and abnormal homeostatic mechanisms. They may be produced by diverse cell types and exert their function on a variety of cells [31]. Their effects (which may be suppressive or enhancing) are on cellular proliferation, differentiation, activation, and motility. In addition, cytokines can exert cytodestructive effects on infectious agents or tumor cells, either directly or by activating cells with cytodestructive potential [112]. Any given cytokine may have many different biologic effects.

The mode of action of many of the cytokines involves typical signal transduction events such as protein phosphorylation, and to date there is only limited understanding of the mechanisms that lead to one activity over another when a specific cytokine is involved in a specific biologic reaction. Nevertheless, elucidation of their role in other pathologic processes has provided insight into autoimmune and allergic diseases, as well as a variety of systemic disorders. Because of their broad spectrum of activity, cytokines have been used in a variety of therapeutic settings involving both infectious diseases and neoplasia [31].

Several lines of evidence have revealed that cytokines play important roles not only in tissue homeostasis but also in the pathogenesis of many infectious diseases. Cytokines play crucial roles in the maintenance of tissue homeostasis, a process which requires a delicate balance between anabolic and catabolic activities.

Table 4: Cytokine Function [114].

Interleukin					
Cytokine	**Cytokine Receptor**	**Cytokine Source**	**Cytokine Targets**	**Cytokine Main Function**	**Cytokine Disease Association**
IL-1α; IL-1b	IL1RI and IL1R-AcP	Macrophages, many others	Macrophages, thymocytes, CNS, others	Inflammatory; promotes activation, costimulation, and secretion of cytokines and other acute-phase proteins; pyrogenic	↑ = inflammatory bone resorption; gout; promotes Th17 response
IL 1ra (antagonist)	Soluble decoyreceptor:IL1RII and IL1R-AcP			IL-1ra and the soluble decoy receptor complex inhibit IL-1mediated inflammatory responses	
IL-2	IL2Rα, IL2Rb, and IL2Rγ	T cells	T, B, NK cells, and macrophages	Proliferation; enhancement of cytotoxicity, IFNγ secretion, and antibody production	↓ = lymphoproliferative disease and susceptibility to autoimmune disease; reduced Treg development. ↑ = reduced Th17 development.
IL-3	IL3Rα and IL3Rb	T cells, mast cells, eosinophils	Hematopoietic progenitors, macro- phages, mast cells	Differentiation and survival of lymphoid and myeloid compartment	
IL-4	IL5Rα and IL3Rb	Th2 cells	Eosinophils, B cells	Proliferation and activation; hallmark of Th2 effector cells	↓ = eosinophil and B-1 cell deficiency. ↑ = allergic asthma.
IL-6	IL7Rα and IL2Rγ	Thymic stromal cells, bone marrow, and spleen	B cells, T cells, thymocytes	Homeostasis, differentia- tion, and survival	↓ = severe combined immune deficiency (SCID)
IL-9	IL9R and IL2Rγ	T cells (Th2)	T cells, mast cells, neutrophils, epithelial cells	Proliferation; promotes Th2 cytokine secretion	
IL-10	IL10R1 and IL10R2	Differentiated T helper cells, Tregs, B cells, dendritic cells, others	Macrophages, T cells, dendritic cells, B cells	Immune suppression; decreases antigen presentation and MHC class II expression of dendritic cells; down- regulates pathogenic Th1, Th2, and Th17 responses	↓ = immune pathology due to uncon- trolled inflammation. ↑ = inhibits sterile immunity to some pathogens.

IL-11	IL11Rα and gp130	Stromal cells	Hematopoietic stem cells, B cells, megakaryocytes	Proliferation	↑ = exacerbates airway diseases
IL-12 (p35 + p40)	IL12Rb1 andIL12Rb2	Macrophages, dendritic cells, B cells, neutrophils	T cells, NK cells	Differentiation and proliferation; promotes Th1 and cytotoxicity	↓ = impaired Th1 responses and increased susceptibility to intracellular pathogens
IL-13	IL13Ra1,IL13Ra2 and IL4Rα	T cells	B cells, macro-phages, others	Goblet cell activation in lung and gut; proliferation and promotion of IgE production; regulation of cellmediated immunity	↓ = impaired Th2 responses to extracel- lular pathogens and allergens. ↑ = exacerbates airway diseases.
IL-14	Not defined	T cells	B cells	Promotion of B cell growth	
IL-15	IL15Rα, IL2Rb, and IL2Rγ	Broad expression in hematopoietic cells	T cells, NK cells, epithelial cells, others	Proliferation and survival; cytokine production	↓ = deficiency in NK cells and defective generation of memory T cells
IL-16	Not defined	T cells, eosinophils, mast cells	CD4+ T cells	Recruitment of CD4+ T cells	
IL-17A	IL17RA or IL17RC	Th17 cells and others	Mucosal tissues, epithelial and endothelial cells	Proinflammatory; protective immunity in lung; tight junction integrity; promotes mobilization of neutrophils and cytokine production by epithelial cells; promotes angiogenesis	↓ = susceptibility to extracellular pathogens ↑ = exacerbates organ-specific autoimmune inflammation
IL-17B		Intestine and pancreas			
IL- 17C		thymus and spleen			
IL-17D		T cells, smooth muscle cells, epithelial cells			
IL-17F	IL17RA or IL17RC	Th17 cells	Mucosal tissues, epithelial and endothelial cells	Similar function as IL-17A but with 2 logs lower receptor affinity	Not well defined. ↑ = increases neutrophil recruit- ment at high concentration.
IL-18	IL18R and IL18-R-AcP	Macrophages, others	Th1 cells, NK cells, B cells	Proinflammatory; induction of IFNγ	↓ = impairs Th1 responses
IL-19	IL20R1 and IL20R2	Monocytes, others	Keratinocytes, other tissues	Proinflammatory	↑ = psoriasis
IL-20	IL20R1 or IL22R1 and IL20R2	Monocytes, others	Keratinocytes, other tissues	Proinflammatory	↑ = psoriasis
IL-21	IL21R and IL2Rγ	Differentiated T helper cells (Th2 and Th17 subsets)	T cells, B cells, NK cells, dendritic cells	Proliferation of T cells; promotes differentia- tion of B cells and NK cytotoxicity	
IL-22	IL22R1 and IL10R2;IL22BP	Th1 and Th17 cells, NK cells	Fibroblasts, epithelial cells	Inflammatory, antimicrobial	↑ = psoriasis

IL-23 (p19 + p40)	IL23R and IL12Rb1	Macrophages and dendritic cells	T cells	Inflammatory; promotes proliferation of Th17 cells	↓ = susceptibility to extracellular pathogens. ↑ = exacerbates organ-specific autoimmune inflammation.
IL-24	IL20R1, IL22R1, IL20R2	Monocytes, CD4+ T cells	Keratinocytes		↑ = antitumor effects
IL-25 (IL-17E)	IL17RB	Th2 cells, mast cells	Non-B, non-T, cKit+, FcεR− cells	Promotes Th2 differentiation and proliferation	↓ = impairs Th2 responses to extracellular pathogens such as worms
IL-26	IL22R1 and IL10R2	Activated T cells			
IL-27 (p28 + EBI3)	WSX-1 and gp130	Activated dendritic cells	T cells, others	Induction of early Th1 differentiation by stimulating expression of the Tbet transcrip- tion factor; Inhibition of effector Th17 cel responses by inducing STAT-1dependent blockade of IL-17 production	↓ = immune pathology due to uncontrolled inflamma- tory response
IL-28A/B/IL29 (IFNλ family)	IL28R1 and IL10R2	Activated subsets of dendritic cells?		May promote antiviral responses	
IL-30 (p28 subunit ofIL-27)					
IL-31	IL31Rα and OSM-Rβ	Activated T cells	Myeloid progenitors, lung epithelial cells, keratinocytes	Proinflammatory	↑ = atopic dermatitis; allergic asthma
IL-32				Induces proinflammatory cytokine production	
IL-33	ST2 and IL1R-AcP	Macrophages, dendritic cells	Mast cells, Th2 cells	Costimulation, promotes Th2 cytokine production	↑ = atopic dermatitis, allergic asthma
IL-35 (p35 + EBI3)		Tregs	Effector T cells	Immune suppression	
Tumor Necrosis Factor (TNF)					
TNF alpha	Murine:TNFR,p55;TNFR,p75 Human:TNFR,p60;TNFR,p80	Macrophages, monocytes, T cells, others	Neutrophils, macrophages, monocytes, endothelial cells	Inflammatory; promotes activation and production of acute-phase proteins	↓ = disregulated fever; increased susceptibility to bacterial infection; enhanced resistance to LPS-induced septic shock ↑ = exacerbation of arthritis and colitis
LT alpha	Murine:TNFR,p55;TNFR,p75 Human:TNFR,p60;TNFR,p80	T cells, B cells	Many cell types	Promotes activation and cytotoxicity; development of lymph nodes and Peyer's patches	↓ = defective response to bacterial pathogens; absence of peripheral lymph nodes and Peyer's patches

LT beta	LTbR	T cells, B cells	Myeloid cells, other cell types	Peripheral lymph node development; proinflammatory	↓ = increased susceptibility to bacterial infection; absence of lymph nodes and Peyer's patches ↑ = ectopic lymph node formation
LIGHT	LTbR, DcR3, HVEM	Activated T cells, monocytes, DCs	B cells, NK cells, DCs, other tissue	Costimulatory; promotes CTL activity	↓ = defective CD8 T cell costimulation
TWEAK	Fn14	Monocytes, macrophages, endothelial	Tissue progenitors, epithelial, endothelial	Proinflammatory; promotes cell growth for tissue repair and remodeling	
APRIL	TACI, BAFF-R,BCMA	Macrophages, DCs	B cell subsets	Promotes T cell- independent responses; B cell homeostasis and differentiation	↓ = impaired class switching to IgA
BAFF (BlyS)	TACI, BAFF-R,BCMA	Macrophages, DCs, astrocytes	B cells	B cell maturation and survival	↓ = B cell lymphopenia; defective humoral immunity ↑ = SLE like syndrome
TL1A	DcR3, DR3	Macrophages, endothelial cells	Activated T cells	Promotes proliferation and cytokine production	GITRL
GITRL	GITR	DCs, macrophages, B cells, others	T regulatory cells, activated T cells	Costimulatory	
OX40L	OX40	Activated T cells, B cells, DCs, monocytes	T cells, B cells, DCs	Costimulatory; activation and migration of monocytes	↓ = impaired humoral responses
CD40L (CD154)	CD40	T cells, monocytes, macrophages, others	B cells, APCs	Costimulatory; promotes T cell- dependent responses; B cell differentiation and class switching	↓ = defective antibody responses and germinal center formation; hyper-IgM syndrome ↑ = SLElike syndrome
FASL	FAS, DcR3	Activated T cells, B cells, and NK cells	APCs, many other cell types	Regulatory; pro apoptotic	↓ = lymphoproliferative disease and systemic autoimmunity
CD27L (CD70)	CD27	Activated T cel s, B cells, DCs, monocytes	T cells, activated B cells	Costimulatory	
CD30L (CD153)	CD30	Neutrophils, B cells, macrophages, activated T cells	T cells, B cells	Costimulatory; promotes proliferation and cytokine production	Viral CD30 blocks Th1 response
4-1BBL	4-1BB	Activated T cells, B cells, DCs, monocytes, macrophages	Activated T cells, B cells, DCs	Costimulatory; promotes activation and migration of monocytes	

TRAIL	TRAIL-R1 (DR4), R2(DR5), R3 (DcR1), and R4 (DcR2)	Activated NK cells, T cells	Many cell types	Costimulatory; promotes NK cell functions; proapoptotic	↓ = defective NKmediated antitumor response ↑ = enhanced responsiveness to autoantigens
RANK Ligand(TRANCE)	RANK receptor orosteoprotegrin	T cells and osteoblasts	Osteoclasts, many cell types	Costimulatory; promotes osteoclasto-genesis and cytokine production	↓ = osteopetrosis ↑ = osteoporosis
Other Cytokines					
FLT3 Ligand	Receptor tyrosine kinases	Diverse tissue	DCs, other myeloid cells	Differentiation and proliferation; synergizes with stem cell factor	↓ = impaired hematopoietic stem cell repopulation and B cell precursors
G-CSF	GCSFR dimer	Macrophages, fibroblasts, other tissues	Committed progenitors	Differentiation and activation of granulocytes	↓ = neutropenia
GM-CSF	GM-CSFRα, βc	T cells, macrophages, fibroblasts, others	Macrophages, granulocytes, dendritic cells, and progenitors	Inflammatory; induction of activation; differ-entiation, growth, and survival	↓ = affects alveolar function
IFNα, IFNβ, IFNω	IFNαR1, IFNαR2	Macrophages, fibroblasts, plasmacytoid DCs, others	NK cells, many others	Promotes resistance to viral pathogens; promotes increased expression of MHC class I	↓ = impaired antiviral responses
IFNα, IFNβ, IFNω	IFNαR1, IFNαR2	Macrophages, fibroblasts, plasmacytoid DCs, others	NK cells, many others	Promotes resistance to viral pathogens; promotes increased expression of MHC class I	↓ = impaired antiviral responses
IFNγ	IFNγR1, IFNγR2	Th1 cells, NK cells, CD8 T cells	Macrophages, NK cells, T cells, others	Promotes activation of APCs and cell-mediated immunity; increased MHC class II expression	↓ = susceptibility to intracellular pathogens
LIF	LIFR, gp130	Macrophages, T cells, fibroblasts, uterus, others	Embryonic stem cells, hematopoietic cells, others	Cell survival	↓ = deficient hematopoietic progenitor cells; defective blastocyst implantation
M-CSF	Receptor tyrosine kinases	Monocytes, fibroblasts, others	Committed myeloid progenitors	Differentiation; prolifera- tion and survival	↓ = monocyte deficiency; osteopetrosis
MIF	CD74 trimer, CD44	Macrophages, T cells	Macrophages	Cell migration, DTH response	↓ = susceptibility to Gram-negative bacteria

OSM	LIFR or OSM- Rβ,gp130	Macrophages, fibroblasts, others	Myeloid cells, embryonic stem cells, T cells, others	Differentiation; induction of immune response (early)	
Stem Cell Factor (SCF)	Receptor tyrosine kinases	Bone marrow	Stem cells, mast cells	Activation and growth	↓ = impaired hematopoietic stem cell proliferation and melanocyte production
TGFβ1, TGFβ2, TGFβ3	TGFβR type I, type II, and type III	T cells, DCs, macrophages, others	All leukocyte populations	Regulatory; inhibits growth and activation; Treg maintenance; synergizes with IL-6 to promote Th17	↓ = increased susceptibility to autoimmune disorders ↑ = fibrotic diseases
TSLP Ligand	TSLPR, IL7Rα	Skin, lung, and gut	DCs and other myeloid cells	Promotes Th2 develop- ment (human); B cell development (mouse)	↑ = atopic diseases

Table 5: Features of cytokines [113,115,116].

Cytokine	Cell Source	Cell Target	Primary Effects
IL-1	Monocytes Macrophages Fibroblasts Epithelial cells Endothelial cells Astrocytes	T cells; B cells Endothelial cells Hypothalamus Liver	Costimulatory molecule Activation (inflammation) Fever Acute phase reactants
IL-2	T cells; NK cells	T cells B cells Monocytes	Growth Growth Activation
IL-3	T cells	Bone marrow progenitors	Growth and differentiation
IL-4	T cells	Naive T cells T cells B cells	Differentiation into a T_H2 cell Growth Activation and growth; Isotype switching to IgE
IL-5	T cells	B cells Eosinophils	Growth and activation
IL-6	T cells; Macrophages; Fibroblasts	T cells; B cells Mature B cells Liver	Costimulatory molecule Growth (in humans) Acute phase reactants
IL-8 family	Macrophages; Epithelial cells; Platelets	Neutrophils	Activation and chemotaxis
IL-10	T cells (T_H2)	Macrophages T cells	Inhibits APC activity Inhibits cytokine production
IL-12	Macrophages; NK cells	Naive T cells	Differentiation into a T_H1 cell

IFNgamma	T cells; NK cells	Monocytes Endothelial cells Many tissue cells - especially macrophages	Activation Activation Increased class I and II MHC
TGF-beta	T cells; Macrophages	T cells Macrophages	Inhibits activation and growth Inhibits activation
GM-CSF	T cells; Macrophages; Endothelial cells, Fibroblasts	Bone marrow progenitors	Growth and differentiation
TNF-alpha	Macrophages; T cells	Similar to IL-1	Similar to IL-1

IL = interleukin; GM-CSF = granulocyte-macrophage colony stimulating factor; IFN = interferon; TNF = tumor necrosis factor; TGF = transforming growth factor

CYTOKINES AND THEIR EFFECT ON CELLS

Each cytokine has a matching cell-surface receptor. Subsequent cascades of intracellular signaling then alter cell functions [117]. This may include the upregulation and/or downregulation of several genes and their transcription factors, resulting in the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition [118].

The effect of a particular cytokine on a given cell depends on the cytokine, its extracellular abundance, the presence and abundance of the complementary receptor on the cell surface, and downstream signals activated by receptor binding, these last two factors can vary by cell type. Cytokines are characterized by considerable "redundancy", in that many cytokines appear to share similar functions [119].

It seems to be a paradox that cytokines binding to antibodies have a stronger immune effect than the cytokine alone. This may lead to lower therapeutic doses [120] showing that inflammatory cytokines cause an IL-10-dependent inhibition of T cell expansion and function by up-regulating PD-1 levels on monocytes which leads to IL-10 production by monocytes after binding of PD-1 by PD-L. Adverse reactions to cytokines are characterized by local inflammation and/or ulceration at the injection sites. Occasionally such reactions are seen with more widespread papulareruptions [121].

Table 6: Cytokine Function [122].

Cytokines	Action
Interferon family	Antiviral proteins
Chemokine family	Direct cell migration, adhesion and activation
Tumor necrosis	Regulate inflammatory factor family and immune responses
Interleukin family	Variety of actions dependent upon interleukin and cell type
Haematopoietins	Promote cell proliferation and differentiation
Transforming growth factor beta	Regulation of immune cells family

ROLES OF CYTOKINES IN HEALTH AND DISEASES

Roles of Cytokines in Health

Cytokines and innate immune system

The immune system is a complex network designed to protect the host from both external (such as bacteria and viruses) and internal threats (such as malignant transformation). Cytokines are important mediators of immune responses that allow integration of the behavior of cells in time and geographical location as the immune responses are generated [56].

The immune system is organized into innate and adaptive immune responses, with adaptive immunity further subdivided into two branches, humoral and cell-mediated immunity [95,123,124].

Innate immunity is immediate and rapid. Innate defense mechanisms include neutrophils and macrophages, which, among other functions, can ingest and destroy pathogens. While often effective in protecting the host, innate immunity is associated with damage to host tissue in the context of providing defense. It is also amnestic in that the inciting agent is not specifically recognized by a unique structure and there is no creation of a memory to that agent such that future responses are more efficient [124].

Adaptive immunity is slower in its response to threats. However, it provides two main features that innate immunity lacks: specific antigen recognition and memory that allows rapid recall of original antigen exposure. Host defense is generally provided in two major arms of the adaptive response [95,123,124] Resistance to *Trypanosoma cruzi* infections is critically dependent on cytokine-mediated activation of cell-mediated immune effector mechanisms. The role of IL-10, TNF-α, IFN-γ and IL-12 in controlling *T*. cruzi replication by the innate and specific immune systems of the vertebrate host can be explained already [47].

Over the years it has become clear that cells of the innate (or natural) immune system contribute to the synthesis of the macrophage-activating and regulatory cytokines TNFα, IFN-β and IL-10 in the early phases of infection by several pathogens, as the immune response develops,

antigen-specific TH cells become the most important source of these cytokines. In addition, IL-12 synthesized by infected or LPS-stimulated macrophages, in addition to other actions, stimulates cytokine synthesis by both NK and T helper cells and promotes the activation and expansion of these lymphocyte subpopulations [125]. Reciprocal regulatory interactions among cytokines secreted by the innate and acquired immune systems ultimately control the activation of each system and its cytokine-mediated effector functions.

White blood cells and certain other cells of the immune system produce cytokines when an antigen is detected [126]. There are many different cytokines, which affect different parts of the immune system:

- Some cytokines stimulate activity. They stimulate certain white blood cells to become more effective killers and to attract other white blood cells to a trouble spot [127].
- Other cytokines inhibit activity, helping end an immune response [128].
- Some cytokines, called interferons, interfere with the reproduction (replication) of viruses [129].
- Cytokines also participate in acquired immunity [47].
- Cytokines released from innate immune cells play key roles in the regulation of the immune response [130].
- These intercellular messengers are the source of soluble regulatory signals that initiate and constrain inflammatory responses to pathogens and injury [131].

These include:

- Monokines, cytokines produced by mononuclear phagocytic cells [20].
- Lymphokines, cytokines produced by activated lymphocytes, especially Th cells [18].
- Interleukins, cytokines that act as mediators between leukocytes [132].
- Cytokines are a group of proteins produced by different cells, especially cells of the immune system, either as a response to an immune stimulus or as an intercellular signal after a certain stimulation. Cytokines have a multitude of different biological effects and are very important both in the innate and in the adaptive immune response [133].

Cytokines bind to specific receptors on target cells with high affinity and the cells that respond to a cytokine are either: 1) the same cell that secreted cytokine (autocrine); 2) a nearby cell (paracrine) or 3) a distant cell reached through the circulation (endocrine). Cellular responses to cytokines are generally slow (hours) because they require new mRNA and protein synthesis 1, IL-10, IL-12, type I interferons (IFN-α and IFN-β), IFN-γ, and chemokines [134].

Tumor necrosis factor alpha (TNF-α) is produced by activated macrophages is response to microbes,

especially the lipopolysaccharide (LPS) of Gram negative bacteria. It is an important mediator of acute inflammation. TNF- α also acts on the hypothalamus to produce fever and it promotes the production of acute phase proteins [135].

Interleukin 1 (IL-1) is another inflammatory cytokine produced by activated macrophages. Its effects are similar to that of TNF-α and it also helps to activate T cells [136].

Interleukin 10 (IL-10) is produced by activated macrophages and Th2 cells. It is predominantly an inhibitory cytokine [137].

Interleukin 12 (IL-12) is produced by activated macrophages and dendritic cells. It stimulates the production of IFN-γ and induces the differentiation of Th cells to become Th1 cells. In addition, it enhances the cytolytic functions of Tc and NK cells [138].

Type I interferons (IFN-α and IFN-β) are produced by many cell types and they function to inhibit viral replication in cells. They also increase expression of class I MHC molecules on cells making them more susceptible to killing by CTLs. Type I interferons also activate NK cells [139] .

Interferon gamma (INF-γ) is an important cytokine produced by primarily by Th1 cells, although it can also be produced by Tc and NK cells to a lesser extent [140].

Chemokines are chemotactic cytokines produced by many kinds of leukocytes and other cell types [7].

Cytokines that play a major role in the adaptive immune system include: IL-2, IL-4, IL-5, TGF-β, IL-10 and IFN-γ as mediators of adaptive immunity [141].

Interleukin 2 (IL-2) is produced by Th cells, although it can also be produced by Tc cells to a lesser extent. It is the major growth factor for T cells. It also promotes the growth of B cells [142,143].

Interleukin 4 (IL-4) is produced by macrophages and Th2 cells. It stimulates the development of Th2 cells from naïve Th cells and it promotes the growth of differentiated Th2 cells resulting in the production of an antibody response. It also stimulates Ig class switching to the IgE isotype [144].

Interleukin 5 (IL-5) is produced by Th2 cells and it functions to promote the growth and differentiation of B cells and eosinophils. It also activates mature eosinophils [145].

Transforming growth factor beta (TGF-β) is produced by T cells and many other cell types. It is primarily an inhibitory cytokine. It inhibits the proliferation of T cells and the activation of macrophages. It also acts on PMNs and endothelial cells to block the effects of pro-inflammatory cytokines [146].

Some cytokines stimulate the differentiation of hematopoetic cells. These include GMCSF which promotes the differentiation of bone marrow progenitors, M-CSF, which promotes growth

and differentiation of progenitors into monocytes and macrophages and G-CSF, which promotes production of PMNs [147].

Soluble antibody can compete with antigen receptors on B cells and block or prevent B cell activation. In addition antigen antibody complexes can bind to Fc receptors on B cells, sending an inhibitory signal to B cells [148].

The release of cytokines is central to almost every stage of the immune response to allergens. During the induction phase, the differentiation of naïve T cells into T helper type 2 cells (Th2), enhances the secretion of IL-4 which stimulates clonal expansion. IL4, IL-9, IL-13 induce goblet cell hyperplasia and promote mucus production. IL-4 and IL13 also affect B cells to produce allergen specific antibodies.

Cytokine production is important for both the early and late phases of the asthmatic reaction. During the early phase reaction, allergen re-exposure triggers the release of cytokines that cause immediate hypersensitivity (IL-3, IL-4, IL-9, IL-13). During the late phase reaction, Th2- and mast cell-derived cytokines (IL-3, IL-5, GM-CSF) stimulate eosinophil activation and leukocyte recruitment to the site of allergen exposure. Finally, cytokine actions are important for the excessive inflammation and airway remodeling that characterizes late phase asthmatic reactions (IL-5, IL-9, IL-13, TNF) [149].

An enhanced Th2 immune response and the elaboration of cytokines such as IL-4, IL13, and IL-5 contribute to the induction of allergy and asthma. Interferon-γ, a Th1 cytokine, acts in conjunction with Th2 (IL-4, IL-13, and IL-5) in maintaining chronic allergic inflammation. The mechanisms leading to an enhanced Th2 response are still controversial. Th2-dominated immune responses may result from immune suppression of T-regulatory cells as well as Th1 cells. Understanding early-life immune mechanisms responsible for atopic diseases, specifically how cytokines of T-regulatory cells act to balance the Th1 and Th2 immune response, continues to be a fruitful area of research [150].

Table 7: Characteristics of cytokines implicated in the innate response [115].

Cytokine	Structure	Producing cell	Function
IL 1	Monomer (18 kD)	Macrophages	Elevation of the temperature T Lymphocytes and Macrophages Activation
IL 6	Monomer (26 kD)	Lymphocytes Macrophages	T and B Lymphocytes activation
IL 12	Heterodimer (75kD)	Neutrophils Macrophages	Lymphocytes differentiation NK cells activation
IL 16	Homotrimer (13kD)	T Lymphocytes	Chemotaxis
TNF α	Homotrimer (17kD)	Macrophages Lymphocytes N cells Mastocytes	Local inflammation Permeability Heat changes
IFN α	Monomer (18kD)	Lymphocytes	SLA I activation
IFN α	Monomer (20kD)	Fibroblasts Other cells	NK cell activation Inhibition of viral replication
IFN α	Homodimer	Lymphocytes NK cells	SLA I and SLA II induction Antigen presentation

DIAGNOSTIC USE OF CYTOKINES

The use of specimen as diagnostic bio-fluid has many advantages over other specimens like blood, exfoliated cells, and urine. It comprises a non-invasive, easy, and rapid to collect, and yet, a cost-effective specimen. Plasma levels of various cytokines may give information on the presence, or even predictive value of inflammatory processes involved in autoimmune diseases such as rheumatoid arthritis [151] as well as immunomodulatory effects of foods or drugs [152]. In addition, elevated levels of IL-7, an important cytokine involved in T cell homeostasis, have been detected in the plasma of HIV-infected patients [153]. It has been proven that certain cytokines are produced by oral squamous cell carcinoma (OSCC) cells. Among these are interleukins (IL)-1, -6, -8, and tumor necrosis factor (TNF)-α [154,155]. When the validity of IL-8 and -6 as biomarkers for OSCC diagnosis has been investigated, analysis of their levels in saliva of a group of 32 patients and 32 healthy controls, and in serum of 19 patients and 32 healthy controls, revealed high sensitivity and specificity of using salivary IL-8 and serum IL-6 levels simultaneously for predicting OSCC [156]. Enzyme-linked immunosorbent assay (ELISA) has been used to investigate the differences in salivary levels of TNF-α, IL-1α, IL-6, and IL-8 between a group of nine patients with OSCC and matching healthy controls [157]. The difference in the salivary level of TNF-α, IL-1α, IL-6, and IL-8, using ELISA, to differentiate between malignant (n = 13) and premalignant (n = 13) lesions, in comparison to healthy subjects [158]. Rhodus et al. 2005 [159] suggested that it is possible to monitor the malignant transformation of premalignant oral lesions by using salivary levels of these cytokines. Serum soluble interleukin-6 receptor (sIL-6R) concentrations were measured in 50 patients with plasma cell dyscrasias using a commercially available immunoenzymatic assay kit.

They conclude that elevated serum sIL-6R levels should be related to the growth of myeloma cells and suggest that serum sIL-6R concentrations may be used as an indicator of disease activity [160].

Cytokines are a unique class of intercellular regulatory proteins that play a crucial role in initiating, maintaining, and regulating immunologic homeostatic and inflammatory processes. Indeed, measurement of cytokine profiles in patients provides a useful indication of disease status. Due to their multiple functions, including regulatory and effector cellular function in many diseases, these molecules, their receptors, and their signal transduction pathways are promising candidates for therapeutic interference [161].

The novel IFN-like cytokines augmented the antiviral activity of IFN-α against several RNA viruses, including encephalomyocarditis virus, vesicular stomatitis virus, and influenza virus in susceptible cell lines. Overall, the study reports a large-scale analysis of cytokines for enhancing the IFN response, and identified cytokines capable of enhancing Stat1, IFN-induced gene expression, and antiviral activities [162].

THERAPEUTIC USES OF CYTOKINES

Cytokines regulate many aspects of cell growth and differentiation and play pivotal roles in the orchestration of immune defense against invading pathogens [163]. The chemokine system in cancer therapy acts as we know that chemokines are a key component of cancer-related inflammation. Chemokines and chemokine receptors are downstream of genetic events that cause neoplastic transformation and are components of chronic inflammatory conditions, which predispose to cancer. Components of the chemokine system affect in a cell autonomous or non-autonomous way, multiple pathways of tumor progression include: leukocyte recruitment and function; cellular senescence, tumor cell proliferation and survival, invasion and metastasis [164]. Components of the chemokine system affect multiple pathways of tumor progression including: leukocyte recruitment, neo-angiogenesis, tumor cell proliferation and survival, invasion and metastasis [165].

Chemokines and chemokine receptors are being investigated for their role in tumor development and metastasis and may prove to be useful therapeutic targets. The chemokine family is a complex network of molecules that are ubiquitously expressed and perform a variety of functions most notably regulating the immune system [166].

Ben-Baruch, 2006 [167] stated that the multifaceted roles of chemokines in malignancy, addressing four major aspects of their activities: (1) inducing leukocyte infiltration to tumors and regulating immune functions, with emphasis on tumor-associated macrophages (and the chemokines CCL2, CCL5), T cells (and the chemokines CXCL9, CXCL10) and dendritic cells (and the chemokines CCL19, CCL20, CCL21); (2) directing the homing of tumor cells to specific metastatic sites (the CXCL12-CXCR4 axis); (3) regulating angiogenic processes (mainly the ELR(+)-CXC and

non-ELR-CXC chemokines); (4) acting directly on the tumor cells to control their malignancy-related functions. Pro-inflammatory cytokines, such as interleukin-1b (IL-1b), interleukin-6 (IL-6) and tumor necrosis factor- (TNF-a) play an essential role in the regulation of immune response and may have prognostic significance in cancer. There was a correlation between IL-1b and sTNF-RI. IL-6 and IL-1b correlated with CRP levels. The mean concentrations of SCC were also elevated. IL-6 and sTNF-RI seemed to be the most sensitive parameters in early stages and may be used as additional markers in oral cancer [168,169] indicated that cytokines and soluble cytokine receptors, both physiologically involved in bone destruction and bone formation, have an essential role in the progression of malignant bone tumors.

Strong correlations between the occurrence of hematological abnormalities and elevated serum levels of several cytokines and soluble cytokine receptors, suggest that the former may develop as a result of cytokine misbalance frequently detected in soft tissue sarcoma patients. However, the results of routine blood tests alone are no independent prognostic factor for survival of soft-tissue sarcoma patients [170].

The majority of studies indicate that interferons are used mainly in the immunotherapy for multiple myeloma, whereas many clinical trials should still be required for the evaluation of the effectiveness of anti-I-L6 antibodies or antiidiotypic vaccines in reference to the eligible patients for these particular therapies [171].

The therapeutic administration of cytokines, modulation of cytokine action, or at times gene therapy is being used for a wide range of infectious and autoimmune diseases, in immunocompromised patients with AIDS, and in neoplasia [161].

Cytokines are often involved in several developmental processes of immune system during embryogenesis. The Cytokine cross-talk between mother and the embryo/ placenta [155,172]. Cytokines are take part in fighting off infections and in other immune responses as proinflammatory [173]. Cytokines have been effect adverse in many disease states schizophrenia, major depression [174], Alzheimer's disease [175,176] . Another important example of cytokine storm is seen in acute pancreatitis [177,178]. Cytokines are integral and implicated in all angles of the cascade resulting in the systemic inflammatory response syndrome and multi organ failure associated with this intra-abdominal catastrophe [179].

Some cytokines have been developed into protein therapeutics using recombinant DNA technology [4]. Recombinant cytokines being used as drugs [180] include:

- Bone morphogenetic protein (BMP), used to treat bone-related conditions [181].
- Erythropoietin (EPO), used to treat anemia [182].
- Granulocyte colony-stimulating factor (G-CSF), used to treat neutropenia in cancer patients [183].

- Granulocyte macrophage colony-stimulating factor (GM-CSF), used to treat neutropenia and fungal infections in cancer patients [184].
- Interferon alfa, used to treat hepatitis C and multiple sclerosis [185].
- Interferon beta, used to treat multiple sclerosis [186].
- Interleukin 2 (IL-2), used to treat cancer [187].
- Interleukin 11 (IL-11), used to treat thrombocytopenia in cancer patients [188].
- Interferon gamma is used to treat chronic granulomatous disease [189] and osteopetrosis [190].

Cytokines have been widely tested in clinical trials during recent years and beneficial responses have been observed in a variety of malignant, infectious and autoimmune diseases. Interferon-alpha induces remissions in patients with certain hematological malignancies such as hairy cell leukemia and chronic myelogenous leukemia. A proportion of patients with chronic viral hepatitis is cured upon application of interferon alpha. Treatment with interferon-gamma reduces the number of infections in patients with chronic granulomatous disease. In addition, several chronic infections with intracellular pathogens also respond to treatment with this cytokine. With the exception of some patients with renal cell carcinoma and malignant melanoma, solid tumors are largely resistant to administration of these cytokines. Cytokine treatment has changed the outlook for a small group of patients with selected chronic diseases [191].

Alpha-interferons have been widely used as a therapeutic agent. Interferons alpha have antiviral, anticancer and immunomodulatory activities. Clinical trials have proved interferons alpha to be of special value as adjuvant therapy (first line drugs) for hairy cell leukemia, virus hepatitis B and C and condylomata acuminata. Interferon alpha is an important advanced modality in the management of chronic myelogenous leukemia and can be considered a first-line therapy option in patients who cannot receive or relapse following allogenic bone marrow transplant. Clinical trials have proved interferons alpha to be of special value as first line drugs for hairy cell leukemia, virus hepatitis B and C and condylomata accuminata. Interferon alpha is used as single primary therapy, adjuvant therapy and maintenance therapy. The limiting factor for the application of interferons alpha is the cost of treatment [192].

Two forms of alpha interferon, interferon alfa-2b and interferon alfa-2a, has been approved for used in Australia. Interferon alfa-2b can be use in the management of hairy cell leukaemia and condylomata acuminata and interferon alfa-2a is use in the management of hairy cell leukaemia and human immunodeficiency virus (HIV) related Kaposi's sarcoma. Applications have been lodged for the use of interferon alfa-2b in HIV related Kaposi's sarcoma, cutaneous basal cell carcinoma and hepatitis B and C and for the use of interferon alfa-2a in the management of hepatitis B, cutaneous T-cell lymphoma and metastatic renal cancer. Interferon alfa-n1 is not

available in Australia except for use in a clinical trial in patients who are HIV seropositive. The use of the alpha interferons is currently under investigation in a wide variety of other diseases, with the likelihood that other indications will soon be established. However, the alpha interferons are generally not regarded as first line agents. Beta and gamma interferons have been studied less intensively than the alpha interferons, but it is likely that selected applications for their use will also be defined with the passage of time [193].

The emergence of genetically engineered biological agents opened new prospects in the treatment of autoimmune and inflammatory diseases. Cytokines responsible for regulation of a wide range of processes during development of the normal immune response are among the most successful therapeutic targets [194].

Saad, 2015, [195] indicated a complex interplay of oxidative stress, endothelial dysfunction, and activation of fibrogenic and inflammatory cytokines as a result of atherosclerosis, hypoxia, and renal hypoperfusion in this disorder. Human studies emphasize the limits of the kidney adaptation to reduced blood flow, eventually leading to renal hypoxia with activation of inflammatory and fibrogenic pathways.

Post-traumatic arthritis (PTA) progression is mediated by the upregulation of proinflammatory cytokines, such as interleukin-1 (IL-1) or tumor necrosis factor-α (TNF-α). Although these cytokines provide potential therapeutic targets for PTA, intra-articular injections of anti-cytokine therapies have proven difficult due to rapid clearance from the joint space. They found that IL-1 plays a critical role in the pathogenesis of PTA following articular fracture, and sustained intra-articular cytokine inhibition may provide a therapeutic approach for reducing or preventing joint degeneration following trauma [196].

The pro-inflammatory cytokines are the prime targets of the strategies to control rheumatoid arthritis (RA). For example, the neutralization of TNFα, either by engineered anti-cytokine antibodies or by soluble cytokine receptors as decoys, has proven successful in the treatment of RA. The activity of pro-inflammatory cytokines can also be down regulated either by using specific siRNA to inhibit the expression of a particular cytokine or by using small molecule inhibitors of cytokine signaling [197].

The anti-IL-17 antibody secukinumab and the anti-IL-2 receptor antibody daclizumab were not superior to placebo for ocular Behçet's in randomised controlled trials, comprising 118 and 17 patients, respectively. The anti-IL-1 agents anakinra and canakinumab and the anti-IL-6 agent tocilizumab were given to isolated refractory disease patients, who were either anti-TNF naïve or experienced. Collectively, it seems that IL-1 and IL-6 are promising targets in patients refractory or intolerant to other regimens including anti-TNFs. However, controlled studies are surely needed [198].

Novel treatments in development for rheumatoid arthritis target 3 broad areas: cytokines, cells, and signaling pathways [199]. Intra-articular IL-1, rather than TNF-α, plays a critical role in the acute inflammatory phase of joint injury and can be inhibited locally to reduce post-traumatic arthritis following a closed articular fracture. Targeted local inhibition of IL-1 following joint injury may represent a novel treatment option for Post-traumatic arthritis [200]. Due to the crucial role of inflammatory cytokines in the pathogenesis of autoimmune disorders, anti-cytokine treatment has been developed as atherapy for rheumatoid arthritis, juvenile idiopathic arthritis (JIA), and inflammatory bowel diseases [201,202]. Dischereit and Lange, 2014 [203] explained early interventions to preserve bone health, for example, by anti-cytokine therapy. In Psoriasis could be more effective of IL-10, IL-23 and efficient [204].

The serum level of IL-17A might prove useful as a biological parameter to ascertain the effectiveness of SLIT for patients with SAR-JCP. It is necessary to produce new therapeutics for non-responders in whom serum IL-17A levels are still higher against long-term SLIT [205].

There is much interest in potential therapeutics that promote remyelination and here we explore use of leukaemia inhibitory factor (LIF), a cytokine known to play a key regulatory role in self-tolerant immunity and recently identified as a pro-myelination factor [206].

Börschel et al., 2015 [207] investigated the efficacy of L19-IL2, an antibody-cytokine fusion protein that specifically delivers IL-2 to the tumor site by homing to the extra-domain B of fibronectin (EDB-Fn) expressed on tumor-associated blood vessels, against mantle cell lymphoma (MCL) in mice. They provide the scientific rationale for the clinical evaluation of L19-IL2 in combination with anti-CD20 immunotherapy in patients with MCL. The experimental model used in this study shown to be appropriate for creation of acute pancreatitis. It was concluded that oleuropein as a prophylactic treatment has no protective effect on serum proinflammatory and anti-inflammatory cytokines as well as pancreatic tissue. Microsecond Pulsed Electric Fields (μsPEFs) inhibits HCC growth in the nude mice by causing mitochondria damage, tumor necrosis and non-specific inflammation. μsPEFs treats porcine livers without damaging vital organs. μsPEFs is a feasible minimally invasive locoregional ablation option [208].

Bladders and kidneys of AKB-4924 treated mice developed less inflammation as evidenced by decreased pro-inflammatory cytokine release and neutrophil activity. They concluded that HIF-1α transcriptional regulation plays a key role in defense of the urinary tract against UPEC infection, and pharmacological HIF-1α boosting could be explored further as an adjunctive therapy strategy for serious or recurrent UTI [209].

Tumor necrosis factor α (TNF-α) is a proinflammatory cytokine that has been implicated in the airway pathology of asthma and result in resistance to hormone therapy. Tumor necrosis factor α inhibitors have become a major research focus in the treatment of asthma. The soluble extracellular region of TNF receptor 1 and Fc fragment of IgG was able to functionally antagonize

TNF-α in vitro and showed promise as a therapeutic agent for the localized treatment of severe refractory asthma [210].

Santos Savio et al., 2015 [211] found a high inter-individual variability in the levels of TNFalpha, IL-6, IL-15 and IL-15 Ralpha in SF of RA patients and were identified four principal clusters of cytokines concentration in SF, suggesting the importance of identifying disease subset of patients for personalized treatment. Finally, they found a correlation between IL-15Ralpha-IL-6, IL-15Ralpha-IL-15, but we did not find any correlation between other pairs of studied cytokines in SF.

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